EFFECT OF PARP INHIBITORS ON TRAIL-INDUCED CELL DEATH IN GLIOBLASTOMA CELL LINES

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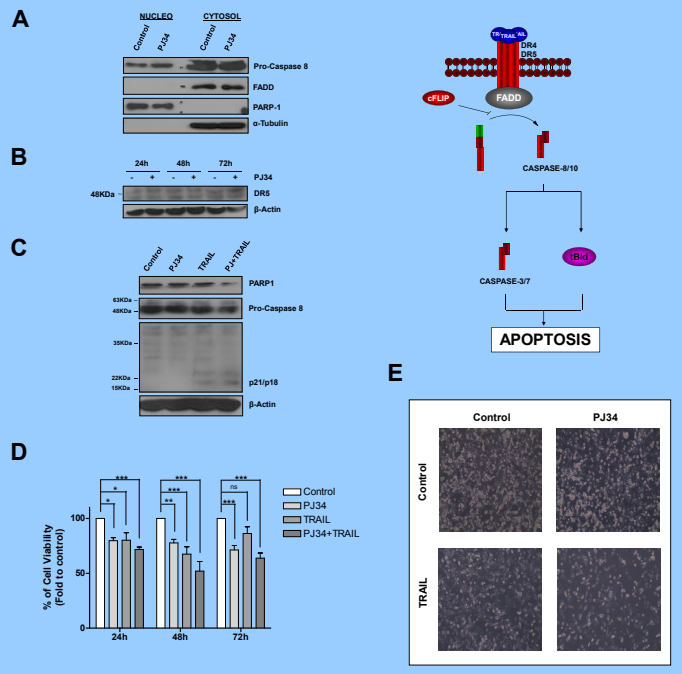
STATE OF THE ART: TRAIL (Tumor necrosis factor-related apoptosis-inducing ligand) has been proved to be an effective anti-neoplastic agent in pre-clinical trials. However, cells from Glioblastoma (GBM, most common and lethal brain tumor) are resistant to this therapy. Therefore, the research of new combined therapies which enhance the effect of TRAIL could probably offer an interesting alternative option. PARP1 has been shown to modify and inactivate DISC components impairing TRAIL-induced cell death.

AIM: to investigate the capacity of PARP inhibitors to enhance TRAIL effect on glioblastoma cell lines.

RESULTS: We have characterized the astrocitoma (grade III WHO classification) SW1783 cell line for the expression of c-FLIP, FADD, Caspase 8 and DR5 (TRAIL receptor). This cell line does not express c-FLIP (data not shown) and presented a nuclear Caspase 8 pool. On the other hand, PJ34 (PARP inhibitor) produced an increase of DR5 after 72 hours of treatment, PARP inhibitor increased TRAIL effect and Caspase 8 activation and PARP knockdown of LN229 glioblastoma cell line (grade IV WHO classification) also increased TRAIL effect and caused Caspase 8 activation.

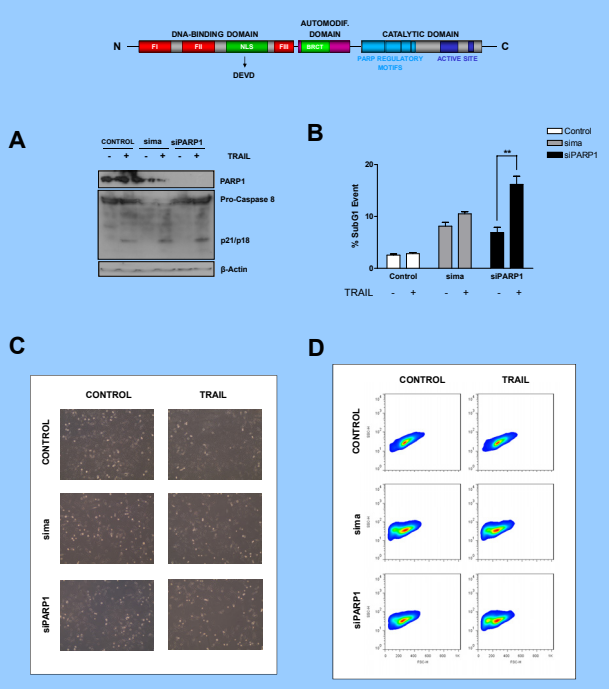
CONCLUSIONS: PARP inhibition /PARP1 knockdown potentiated TRAIL-induced cell death in different glioblastoma cells. Mechanistically this potentiation could be due to the amplification of TRAIL signalling through increasing DR5 and optimisation of caspase 8 activation.

Fig 1. EFFECT OF PARP INHIBITORS ON TRAIL PATHWAY IN GBM



A. Measurement of Pro-Caspase 8, FADD and PARP1 after PARP inhibition by cytosol-nucleus subfraction: SW1783 GBM cell line was treated 24 hours with PJ34 (PARP inhibitor) 10μM. **B. Measure of DR5 levels after PARP inhibition:** SW1783 was treated 24, 48 and 72 hours with PJ34 10μM. C. **Caspase 8 activation after PJ34-TRAIL combination treatment:** SW1783 cells was treated 48 hours with TRAIL (500ng/ml) and PJ34 (5μM). **D and E. Effect of PJ34-TRAIL combination on cell viability**: SW1783 was treated 24, 48 and 72 hours with PJ34 (10μM) and TRAIL (500ng/ml).

Fig 2. EFFECT OF PARP KNOCKDOWN ON TRAIL PATHWAY IN GBM



A. Measurement of Caspase 8 activation in LN229 GBM cells PARP1 knockdown after 48 hours of TRAIL treatment (500ng/ml) . B, C and D. Measure of cell death in LN229 GBM cells PARP1 knockdown treated 48 hours with TRAIL (500ng/ml).

Perspectives:

- Study the molecular interaction between PARP1 or PARylation with TRAIL components
- In vivo experiments to test the effect in preclinical mouse models with orthotopic brain tumor.
- Extend these observation to other glioblastoma cell lines, including primary, patient-derived glioma cells

References:

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